

## **REMARKS**

Claims 46-52, 54, 58-59 and 61-70 are pending in the present application. Claims 54, 61 and 62 have been withdrawn by the Examiner as being drawn to a nonelected species.

Applicants have amended claims 58, 59 and 65 to correct the dependency of claims in view of previously canceled claims. Claims 58 and 59 have been further amended to also depend upon claim 54. Support for these amendments can be found in the specification, for example, at page 10, line 31 to page 11, line 4 and page 12, lines 5-8.

No new matter has been added by these amendments. Upon entry of these amendments, claims 46-52, 54, 58-59 and 61-70 will be pending in the present application.

Applicants respectfully request that the amendments and remarks made herein be entered and fully considered.

### **The Rejections Under 35 U.S.C. § 103(a) Should be Withdrawn**

Claims 46, 49-52, 58, 59 and 63-70 were rejected under 35 U.S.C. § 102(a) as allegedly being obvious over by U.S. Patent No. 6,146,632 (the “‘632 patent”) in view of U.S. Patent No. 4,727,064 (the “‘064 patent”). Applicants respectfully disagree with the Examiner’s rejection and submit that the rejection should be withdrawn for the reasons discussed below.

The Examiner contends that the ‘632 patent teaches a method of enhancing an immune response with an immunogenic composition comprising an antigen (from polypeptide, glycoprotein or lipoprotein from bacterial or viral sources) and QS-21. The Examiner notes that the ‘632 patent does not teach beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin.

The Examiner contends that the ‘064 patent teaches that hydroxypropyl-beta-cyclodextrin (HPCD) improves solubility which reduces the tendency to cause irritation and that HPCD stabilizes a wide range of drugs, exhibits low toxicity, extends shelf life and is widely used as an excipient.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ HPCD as an excipient (as taught by the ‘064 patent) in an immunogenic composition comprising QS-21 and an antigen (as taught by the ‘632 patent). The Examiner alleges that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because the ‘632 patent

teaches that HPCD adds stability to any drug and extends shelf life, reduces irritation and exhibits low toxicity. The Examiner further alleges that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

The legal standard for nonobviousness was presented in Applicants' Amendment Under 37 C.F.R. 1.111 filed on April 11, 2005.

With respect to the bases for the Examiner's rejection, Applicant respectfully disagrees and submits that the presently claimed invention is not obvious because the art cited by the Examiner provides no suggestion or motivation to use a beta-cyclodextrin with a saponin adjuvant.

The '632 patent describes the use of oil in water emulsions as vaccine formulations. See '632 patent, col. 1, lines 3-6. The oil in water emulsions may be used together with vaccines comprising QS21. See id., col. 1, lines 9-13. There is no teaching, suggestion or motivation in the '632 patent to use a composition comprising a saponin adjuvant and a beta-cyclodextrin to enhance an immune response to an antigen in an individual. Thus, '632 patent does not render obvious the presently claimed invention.

The '064 patent does not remedy the deficiencies of the '632 patent. The '064 patent describes pharmaceutical preparations consisting generally of a drug with substantially low water-solubility, i.e., that is crystalline, and amorphous, water-soluble cyclodextrin-based mixtures. See the '064 patent, col. 1, lines 8-11 and 50-56. These cyclodextrin mixtures solubilize the crystalline drugs and have very low toxicity. See id., col. 2, lines 44-59. Notably, it is the cyclodextrin mixtures themselves that have very low toxicity. See id., col. 4, line 57 to col. 5, line 13. There is no teaching or suggestion that the cyclodextrin mixtures can reduce the toxicity of the drugs. Furthermore, contrary to the Examiner's assertion that the '064 patent teaches that HPCD is widely used as an excipient, Applicant can find no teaching or suggestion in the '064 patent that HPCD can be used with anything except drugs with substantially low water solubility that tend to crystallize. Applicants respectfully submit that there is no motivation to combine the '064 patent, which teaches the use of cyclodextrin mixtures to improve the solubility of drugs with substantially low water-solubility, with the '632 patent, which teaches vaccine formulations that are oil-in-water emulsions in combination with QS21 to enhance immune responses to a given antigen. There is no teaching or suggestion that antigens or saponin adjuvants tend to crystallize and have poor water solubility, or that such is a concern in immunization procedures. For the above reasons, the '064 patent does not teach or suggest or provide a motivation for using a beta-cyclodextrin in combination with a saponin adjuvant. Thus, the '064 patent, whether alone or

in combination with the '632 patent, does not render obvious the presently claimed invention. Accordingly, the references cited by the Examiner do not provide a *prima facie* case of obviousness.

Even assuming, *arguendo*, that the '632 patent and the '064 patent could be properly combined, Applicants respectfully submit that unexpected results are provided. The present invention demonstrates that the combination of a saponin adjuvant and a beta-cyclodextrin reduces the lytic effect of QS-21, QS-7 and Quil-A (see Examples 1 and 2). Notably, this effect was only seen with beta-cyclodextrins, and not with  $\alpha$ -cyclodextrin or hydroxypropyl- $\gamma$ -cyclodextrin. See Example 1. The combination of QS-21 and hydroxypropyl-beta-cyclodextrin also improved tolerance to QS-21 adjuvant associated pain in humans. See Example 6 and Figures 5 and 6. These improved properties would not be expected by one of skill in the art, and they provide evidence of nonobviousness of the invention.

Claims 46-52, 58, 59 and 63-70 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the U.S. Patent No. 5,057,540 (the “‘540 patent”) in view of the '064 patent. Applicants respectfully disagree with the Examiner’s rejection and submit that the rejection should be withdrawn for the reasons discussed below.

The Examiner contends that the '540 patent teaches a method for enhancing immune response with an immunogenic composition comprising a peptide antigen (such as gp70) and a saponin adjuvant (wherein the saponin can be QA-17, -17, -18, -21 and Quil-A) in a human. The Examiner notes that the '540 patent does not teach beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin.

The Examiner contends that the '064 patent teaches that hydroxypropyl-beta-cyclodextrin (HPCD) improves solubility which reduces the tendency to cause irritation and that HPCD stabilizes a wide range of drugs, exhibits low toxicity, extends shelf life and is widely used as an excipient.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ HPCD as an excipient (as taught by the '064 patent) in an immunogenic composition comprising QS-21 and an antigen (as taught by the '540 patent). The Examiner alleges that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because the '632 patent teaches that HPCD adds stability to any drug and extends shelf life, reduces irritation and

exhibits low toxicity. The Examiner further alleges that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

With respect to the bases for the Examiner's rejection, Applicant respectfully disagrees and submits that the presently claimed invention is not obvious because the art cited by the Examiner provides no suggestion or motivation to use a beta-cyclodextrin with a saponin adjuvant.

The '540 patent describes the use of substantially pure saponins as adjuvants. Immunologic compositions are also provided comprising a saponin adjuvant in combination with an antigen component. The '540 patent describes the use of saponins, optionally, with non-saponin adjuvants and/or inert carriers. See, e.g., the '540 patent, col. 7, lines 20-31 and col. 8, lines 7-11. There is no teaching, suggestion or motivation in the '540 patent to use compositions comprising saponins and a beta-cyclodextrin to enhance an immune response to an antigen in an individual. Thus, the '540 patent does not render obvious the presently claimed invention.

The '064 patent does not remedy the deficiencies of the '540 patent. As discussed above, the '064 patent describes the use of cyclodextrin mixtures to improve the solubility of drugs with substantially low water-solubility. Applicants respectfully submit that there is no motivation to combine the '064 patent, which is directed to delivering a drug with substantially low water-solubility using cyclodextrin mixtures to improve the solubility of drugs, with the '540 patent, which is directed to delivering an antigen to which an immune response is desired using a saponin adjuvant to enhance the immune response. There is no teaching or suggestion that antigens or saponin adjuvants tend to crystallize and have poor water solubility, or that such is a concern in immunization procedures. For the above reasons, the '064 patent does not teach or suggest or provide a motivation for using a beta-cyclodextrin in combination with a saponin adjuvant. Thus, the '540 patent, alone or in combination with the '064 patent, does not render obvious the presently claimed invention.

Moreover, as described above, Applicants have provided unexpected results to overcome any *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

**CONCLUSION**

Applicants respectfully request that the present amendments and remarks be made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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